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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/090,983	03/04/2002	William C. Manning JR.	20263.50	7567

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/090,983	MANNING ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-34 and 42-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-34 and 42-49* is/are rejected.

7)☒ Claim(s) *42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/4 and 13/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 11/13/2003 has been entered. Claims 35-41 have been cancelled. Claims 30, 34 and 42 have been amended. Claims 45-49 have been added. Claims 30-34 and 42-49 are pending and under consideration in the instant action.

Specification

In light of Applicant's amendments to the Abstract and the specification, the objection to the specification is withdrawn.

Sequence Compliance

The specification is now sequence compliant.

Claim Objections

Claim 42 is objected to because of the following informalities:

Claim 42 ends with two periods.

Claims 42-44 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to other claims in the alternative only. See MPEP § 608.01(n). Claims 43 and 44 depend from improper claim 42 are included in this rejection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-34 and 42-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-human animal model of neovascularization wherein said model is produced by subretinal administration of an adeno-associated virus vector comprising a nucleic acid encoding an angiogenic factor and for a method of using said model for evaluating the ability of an anti-angiogenic factor to prevent neovascularization by co-administration of rAAV vectors encoding an angiogenic and an anti-angiogenic factor does not reasonably provide enablement for a non-human animal model wherein the transgene has been introduced intravitreally or for a method of evaluating the ability of an anti-angiogenic factor to inhibit the neovascularization of the eye comprising administering an anti-angiogenic factor to an animal model of neovascularization having neovascularization already present and determining the ability of said anti-angiogenic agent to inhibit neovascularization. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Aspects of the previous rejection are maintained as set forth below.

Applicant's arguments filed 11/13/2003 have been fully considered but they are not persuasive. Applicant has argued on page 7 of the amendment that factors other than VEGF function in induction of angiogenesis (page 7, paragraph 4). Applicant references Ozaki in arguing that there are increased levels of angiogenin in the vitreous of patients with diabetic retinopathy, which is known to involve neovascularization.

In response, Ozaki reports increased levels of angiogenin in the vitreous of patients with diabetic retinopathy but fails to provide a functional link between the presence of angiogenin and neovascularization of the eye. Ozaki states that several possible angiogenic factors, including

VEGF, which is known to be functionally linked to ocular neovascularization in patients with diabetic retinopathy, are also present in the eyes of patients with diabetic retinopathy (paragraph bridging pages 358-359). Accordingly, Ozaki states that that angiogenin is "not a key factor of ocular angiogenesis" and may act as a cofactor or para-factor (page 359, column 2, lines 22-27). Furthermore, evidence of a potential link of only one factor other than VEGF to neovascularization of the eye fails to provide a nexus between the angiogenic potential of VEGF in the eye and any angiogenic factor as claimed. Therefore, the evidence of record fails to support the use of any angiogenic factor in establishing a model of neovascularization as claimed.

Applicant argues that the specification on pages 13-17 provides detailed instructions on using various viral vectors other than adeno-associated viral vectors (page of 8). Applicant argues further that the specification provides detailed information regarding administering gene delivery vectors to subsections of the eye (page 9, paragraphs 1 and 2). Applicant argues that the specification teaches how to deliver the viral vector to the vitreous (see specification, page 28, lines 6-11) and that Example 16, on page 56 of the specification, establishes choroidal neovascularization.

In response, the teachings on pages 13-14 are merely prophetic, listing a number of different retroviruses that can generally be used to deliver DNA to cells. The teachings on pages 14-16 are relevant to adeno-associated viruses. The paragraph spanning pages 16-17 provide general teachings regarding alphavirus vectors, with no specific teachings regarding use for delivering genes to the eye for the purpose of inducing neovascularization. Finally, paragraph 3

on page 17 merely lists a number of viral vectors that can be used in gene delivery. With respect to the intravitreal administration, the specification teaches intravitreal administration only prophetically on page 28. It does not teach an effect of intravitreal administration. Furthermore, Example 16 on page 58 teaches only sub-retinal injection (see page 58, line 15). The specification teaches that subretinal administration delivers AAV to the choroid (page 23, lines 8-13) and intravitreal administration results in infection of retinal vasculature (page 23, lines 13-15). It is not clear how the teachings of choroidal neovascularization in the described eyes, injected subretinally, provide support for intravitreal administration of the VEGF vector.

As set forth in the previous office action, mailed 08/13/2003, it was well known in the art that each gene delivery system has characteristic limitations and viral vectors must be chosen according to desired parameters. The specification has not demonstrated the use of any vector other than an adeno-associated viral vector and has not provided a correlation between an adeno-associated viral vector and any other type of vector that would allow one to overcome the unpredictability associated with the art of gene therapy as outlined on pages 6-7, 9 and 10 (see Verma, 1997; Eck and Wilson, 1996; Romano, 1999; Ali, 1997). Specifically, parameters to consider when making and using a gene delivery vector, include the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced (Verma, 1997, Nature, Vol. 389, pages 239-242).

Romano reiterates this point by noting that that unpredictable factors such as the particular vector system used as well as the *in vivo* expression of the vector have not been shown to have been overcome by routine experimentation (page 194, column 1). The specification does not teach what viral vectors encompassed by the claims are capable of infecting the desired tissues or what dosage must be used in combination with the broad genera of angiogenic factors encompassed by the claims so as to overcome the unpredictability set forth in the art.

With respect to the ability of an anti-angiogenic factor to inhibit ongoing neovascularization of an eye, Applicant argues that the methods of claims 42-44 are directed to a non-human animal model, not a method of treating disease and that the methods are directed to screening for anti-angiogenic factors that have a desired effect (page 10, paragraph 2).

In light of the amendment to claim 30, claim 42 continues to read on administration of an anti-angiogenic factor to an animal model already exhibiting neovascularization (refer to pages 8-12 of the previous office action, mailed 08/13/2003). The specification teaches co-transfection of cells with rAAV encoding VEGF and sFLT-1 or PEDF (page 58). The specification teaches that the co-transfection of sFLT-1 or PEDF prevents the disrupted retinal function normally caused by neovascularization that results from transfection with rAAV encoding VEGF alone. The specification does not teach how to evaluate an anti-angiogenic factor in an animal already exhibiting neovascularization. As set forth in the previous office action, the specification teaches prevention of neovascularization caused by introduction of VEGF (pages 8-9) by co-transfection of cells with an angiogenic and anti-angiogenic factor. Therefore, the guidance is specific to

inhibiting the onset of neovascularization by coadministration of angiogenic and anti-angiogenic factors, not inhibition of neovascularization that has already begun.

Thus, for the reasons given above, it would require undue experimentation for one of skill in the art at the time of filing to implement the invention as claimed with a predictable degree of success. There is insufficient guidance in the specification, in view of the state of the art at the time of filing, to determine that the broadly claimed methods would result in production of an animal model of neovascularization.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30,31,33, 34 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Okamoto (American Journal of Pathology, 1997, Vol. 151, pages 281-291). The rejection set forth on page 13 of the previous office action is maintained and applied to newly added claim 46.

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues that Okamoto teaches a transgenic non-human animal model for neovascularization and that the claimed animal model is not a transgenic but is modified by delivery of a viral vector (see page 10, last paragraph).

Claims are drawn to a non-human animal model of neovascularization comprising a nucleic acid encoding an angiogenic factor in the eye of the animal. The amendments to claim 30

merely alter the process by which the claimed animal model is obtained. Claim 30, therefore, is a product by process claim in which the process of creating the animal carries little patentable weight. It is only the product, which is anticipated by the prior art and not the process by which the product was made. This is because the final product (a non-human animal model of neovascularization comprising a nucleic acid encoding an angiogenic factor in the eye of the animal) is not distinguished by any particular features or characteristics resulting from the process by which it is made. As such, the limitations of the claimed non-human animal model of neovascularization comprising a nucleic acid encoding an angiogenic factor in the eye are met by any non-human animal model of neovascularization comprising a nucleic acid encoding an angiogenic factor in the eye in the prior art. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re* Thorpe, 227 USPQ 964 (Fed. Cir. 1985).

Okamoto taught transgenic mice comprising a VEGF transgene operably linked to the bovine rhodopsin promoter (page 282, paragraph bridging columns 1-2) which drives expression of VEGF to the retina, causing neovascularization of the retina (paragraph bridging pages 285-287). A transgenic mouse comprising a VEGF transgene is an animal having an angiogenic transgene in the eye.

Thus, the teachings of Okamoto anticipate the limitations of claims 30, 31, 33, 34 and 46.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Fri 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

PETER PARAS
PATENT EXAMINER

Valarie Bertoglio
Examiner
Art Unit 1632